

**HED DOC. NO. 013520**

**DATE: June 21, 1999**

**MEMORANDUM**

**SUBJECT: *OXYDEMETON METHYL (ODM)* - REPLACEMENT OF HUMAN STUDY  
USED IN RISK ASSESSMENTS** - Report of the Hazard Identification  
Assessment Review Committee.

**FROM:** Jess Rowland, Co-Chair  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)  
and  
Pauline Wagner, Co-Chair  
Hazard Identification Assessment Review Committee  
Health Effects Division (7509C)

**TO:** Al Nielsen, Branch Senior Scientist  
Reregistration Branch 2  
Health Effects Division (7509C)

**PC Code: 058702**

On February 16, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for ODM and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments and supersedes all other reports (RfD, TES, HIARC, etc) for ODM.**

### Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Karen Hamernik, Pam Hurley, Mike Ioannou, Tina Levine, Nicole Paquette, Kathleen Raffaele, Jess Rowland, PV Shah, Brenda Tarplee (Executive Secretary), and Pauline Wagner. Member in absentia: Susan Makris.

Other HED staff present at the meeting were: Paula Deschamp, William Sette, and Tim Leighton.

---

Brenda Tarplee  
Executive Secretary  
Hazard Identification Assessment Review Committee

## **I. BACKGROUND**

Oxydemeton methyl (ODM) was reviewed by the Health Effects Division-Hazard Identification Assessment Committee (HIARC) on July 1 and 2, 1997 (memorandum dated July 24, 1997) and by the Health Effects Division Toxicology Endpoint Selection (TES) Committee (document dated May 1, 1997).

On February 25, 1998, the HIARC met again to re-evaluate the toxicological endpoints for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments in light of a recently submitted 7-day dermal toxicity study. The HIARC determined that the application of the FQPA safety factor for the protection of infants and children from exposure to ODM, as required by FQPA, will be determined during risk characterization.

In December 10-11, 1998, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In January, 1999, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including oxydemeton methyl. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data were evaluated as follows:

If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x interspecies uncertainty factor.

If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the interspecies uncertainty factor.

On January 14, 1998, using the parameters developed for evaluation of the human studies, the HIARC evaluated the oxydemeton methyl cholinesterase inhibition study in human volunteers (Doull et al, 1972; MRID No. 00039839). The HIARC classified this study as *supplemental*

because the results provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the study alone is not sufficient for endpoint selection or risk assessments due to technical limitations.

On February 16, 1999, HIARC evaluated the doses and toxicology endpoints selected for ODM based solely on animal toxicity studies. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments.

**For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.**

## **II. HAZARD IDENTIFICATION**

### **A. Acute Dietary Reference Dose (RfD)**

Study Selected: Acute Neurotoxicity Study in the Rat §81-8

MRID No. 43929901

Executive Summary: In an acute neurotoxicity study, four groups of 42/sex Sprague-Dawley Crl:CD<sup>R</sup>(SD)BR strain rats were dosed at 0 (control), 2.5, 10 or 50 mg/kg of ODM (dose in terms of a.i., the study report indicates the doses were 5, 20 and 100 mg/kg of a 50% formulation in methylisobutylketone stabilizer) in water by gavage. Animals (12/sex/dose) were assessed for FOB (peak time of effect of 1.5 to 1.75 hours post dosing) and motor activity (1.75-2.25 hours post dosing) and 10/sex/dose were assessed for plasma, RBC and brain cholinesterase (ChE) at the peak time of effect and again on days 7 and 15. At 10 mg/kg there were tremors, ataxic gait and pinpoint pupils, decreases in rearing, arousal response, defecation, visual placement, pinch responses, body temperature and motor activity. At 50 mg/kg there were deaths and some 15 other FOB parameters affected to indicate both motor and sensory impairment and body weight decrease. Plasma (45% ♂, 58% ♀), RBC (38% ♂, 30% ♀) and brain ChE (45% ♂, 39% ♀) were all inhibited at 2.5 mg/kg when assessed at approximately 1.5 hours postdosing. The 10 and 50 mg/kg dose groups showed progressively more inhibition. Brain ChE recovered slowly but remained inhibited at day 15.

Dose/Endpoint for establishing the Acute RfD: LOAEL = 2.5 mg/kg/day, based on inhibition of plasma, RBC, and brain ChE. The NOAEL was not established.

Comments about Study and Endpoint: The endpoint was observed following administration of a single oral dose which is appropriate for this risk assessment.

Uncertainty Factor (UF): UF = 300 (10x for inter-species extrapolation, 10x for intra-species variability, and 3x for the use of a LOAEL).

$$\text{Acute RfD} = \frac{2.5 \text{ mg/kg/day (LOAEL)}}{300 \text{ (UF)}} = 0.008 \text{ mg/kg/day}$$

Comments about study, endpoint and UF **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** The HIARC report dated May 7, 1998 includes the 10x FQPA safety factor in deriving the acute RfD which was not included in the acute RfD shown above. As per the current OPP policy the FQPA safety factor is applied to the acute RfD (not to the LOAEL) to derive a Population Adjusted Dose (PAD).

**This risk assessment is required.**

#### **B. Chronic Dietary RfD**

Study Selected: Chronic Toxicity-Dog §83-1b

MRID No.: 00151805, 41980801 and 43454201)

Executive Summary: Groups of beagle dogs (6/sex/dose) received oxydemeton methyl via intubation at doses of 0.0125, 0.125, or 1.25 mg/kg/day for 52 weeks. Doses were adjusted for individual animal body weights on a weekly basis. The dosing volume was 10 ml/kg; control dogs received 10 ml/kg tap water. Dogs were intubated daily, 1-3 hours before morning feeding. The NOAEL was 0.0125 mg/kg/day and the LOAEL was 0.125 mg/kg/day based on inhibition of plasma, erythrocyte and brain cholinesterase activity in both sexes of dogs.

Dose and Endpoint for Risk Assessment: NOAEL=0.0125 mg/kg based on plasma, erythrocyte and brain cholinesterase inhibition in males and females at 0.125 mg/kg (LOAEL).

Uncertainty Factor: 100 (10x for inter-species variation and 10x for intra-species extrapolation).

$$\text{Chronic RfD} = \frac{0.0125 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.000125 \text{ mg/kg}$$

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC concluded that the 10x inter-species extrapolation factor cannot be modified/alterd. The study in humans (Doull *et al.* 1972) is useful only as *supplemental* data. Although this study provided

supportive scientific data, it is not appropriate for use in risk assessment and the treatment regimen (25-30-days in four subjects and 2 subjects for 60 days) is not adequate to characterize lifetime exposure. Additionally, cholinesterase inhibition did not reach steady state until 2-24 months in rats and there is uncertainty as to when this occurs in humans. There is concern for the occurrence of brain cholinesterase inhibition (not measurable in humans) at the same dose levels as plasma cholinesterase inhibition in animals. Data from the animal studies demonstrate that plasma, red blood cell, and brain cholinesterase inhibition occur at the same dose levels in both sexes of rats (90-day neurotoxicity study) and in dogs (chronic study). Therefore, no comparison of dose and effects in humans and animals could be made.

### C. Occupational/Residential Exposure

There are no registered residential uses at the present time. Therefore, the following risk assessments are applicable only for occupational exposures.

#### 1. Dermal Absorption

MRID No.: 001638631

Dermal Absorption Factor: Dermal absorption was calculated to be 50.4% for males and 51.8% for females. The dermal absorption rates as calculated by regression analysis based on mg equivalents of  $^{14}\text{C}$ -ODM over time were  $0.15 \mu\text{g}/\text{cm}^2/\text{hour}$  for males and  $0.17 \mu\text{g}/\text{cm}^2/\text{hour}$  for females.

#### 2. Short-Term Dermal (1-7 Days)

Study Selected: 7-Day Dermal Toxicity Study in the Rat

MRID No. None assigned (preliminary data submission by the registrant)

Executive Summary: ODM was administered dermally in water to Sprague- Dawley rats (10/sex/dose) at doses of 0, 1.5, 5.0, 10.0 or 20.0 mg/kg/day, 6 hours/day, for 7 days.

All animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Further, no body weight decrements or effects on food consumption occurred. At terminal sacrifice, no treatment-related gross necropsy findings were reported.

At day 7, statistically significant inhibition of RBC and brain ChE activities were observed, plasma ChE activity was not inhibited by treatment. RBC ChE activity of males dosed at 10 and 20 mg/kg/day was inhibited by 12% and 25%, respectively, and brain ChE activity by 8.2 and 12%, respectively. Brain ChE activity in females was inhibited by 14% at 20 mg/kg/day. Plasma ChE activity in males and females and RBC ChE activity in females were comparable to control values.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on significant inhibition of RBC and brain ChE in males (12% and 8.2%, respectively) at 10 mg/kg/day (LOAEL).

Comments about Study and Endpoint: **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** For the 14-day dermal toxicity study, plasma and erythrocyte ChE activities were measured at 7 days and 14 days; while brain ChE activity was measured only at 14 days. In the 7-day dermal toxicity study, plasma, erythrocyte and brain ChE activities were all measured at 7 days. For this reason, the 7-day dermal toxicity study was selected over the 14-day dermal toxicity study. Further, there was no consistency in the results of the two studies (plasma and erythrocyte ChE inhibition at 5 mg/kg/day differed greatly between the two studies). The rationale provided by the Registrant was not adequate to reject the 14-day study as flawed.

**This Risk assessment is required.**

### **3. Intermediate-Term Dermal (7 Days to Several Months)**

Study Selected: 14-Day Dermal Toxicity Study in the Rat

MRID No. 40499304

Executive Summary: ODM (94.6%), was administered dermally in water to five Sprague Dawley rats per sex per group, 6 hour per day, for 14 days at 0, 0.3, 1.0, and 5.0 mg/kg/day. Plasma ChE and RBC ChE activity was determined at day 0, 7, and 14. Brain ChE activity was determined at termination. No effects were seen on body weight or food consumption. No treatment-related clinical findings or necropsy observations were observed. No biologically significant inhibition of plasma or erythrocyte ChE was observed in low-, mid- or high-dose males and females on day 0. At day 7, significant inhibition of plasma and erythrocyte ChE was observed in high-dose males (38% and 26%, respectively) and females (40% and 28%, respectively). At day 14, plasma ChE was inhibited only in high-dose females (55%), while erythrocyte ChE was inhibited in mid-dose females (11%) and high-dose males (37%) and females (46%). Brain ChE activity, measured at day 14, was inhibited in mid- and high-dose males (12% and 48%, respectively) and low-, mid- and high-dose females (11%, 16% and 60%, respectively). Dose and Endpoint for Risk Assessment: NOAEL = 0.3 mg/kg./day for brain ChE inhibition in males.

Comments about Study and Endpoint: **No change from the previous dose/endpoint selected based on the rat study (i.e., human data was not used previously).** This study was conducted via the appropriate route of concern (i.e., dermal) for this risk assessment.

**This Risk assessment is required.**

#### **4. Long-Term Dermal (Several Months to Life-Time)**

Study Selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: Based on the current use pattern, there is minimal concern for long term dermal exposure potential/risk.

**This risk assessment is NOT required**

#### **5. Inhalation Exposure (Any Time Period)**

Study Selected: Acute inhalation study in the rat (81-3)

MRID Nos. 40779805C and 40779805

Executive Summary: In an acute inhalation toxicity study, groups of young adult Sprague Dawley rats were exposed by the inhalation route to ODM (50% concentrate, 55.3% a.i. in 50% polyethylene glycol 400 and 50% ethanol) for 4 hours (nose only) at concentrations of 0.177, 0.224, 0.266, 0.370 or 0.540 mg/L. Animals then were observed for 14 days. The LC<sub>50</sub> for males was 0.443 mg/L and for females was 0.427 mg/L. The NOAEL was <0.177 mg/L or < 0.0979 mg a.i./L based on clinical signs (tremors) in males and females (note: dose levels should be multiplied by 0.553 to adjust for percent active ingredient).

Dose dependent mortality was seen at  $\geq 0.266$  mg/L in males and females. Death occurred on the day of dosing to day 5 after dosing. Most deaths occurred on day 0 to 2, with only 1 male dying on day 5 and 1 female dying on day 3. Tremors were seen in most males and females at all dose levels. In addition, hypoactivity and salivation were seen in most males and females at  $\geq 0.224$  mg/L. Clinical signs ended by day 7. There appeared to be body weight gain decreases in females at  $\geq 0.370$  mg/L and in males at  $\geq 0.224$  mg/L. Single necropsy findings occurred more frequently at  $\geq 0.266$  in males and  $\geq 0.0.370$  mg/L in females, such as salivation, turbinates red, ventrum staining and black zone in the glandular stomach mucosa. No compound related lesions were seen in animals that survived to day 14.

Dose and Endpoint for Risk Assessment: Dose=0.098 mg/L; the LOAEL of 0.177 mg/L adjusted for percent active ingredient ( $0.177 \times 0.553$ ). A NOAEL was not established.



Comments about Study and Endpoints: Since no other inhalation studies were available, the HIARC recommended that this dose be used for short, intermediate and chronic exposure risk assessments. Since a LOAEL was used a MOE of 300 is required for this exposure scenario.

**This Risk assessment is required.**

#### **D. Margin of Exposure for Occupational/Residential Exposures**

There are no residential uses at the present time. For occupational exposure risk assessments, a MOE of 100 is required for dermal exposures and a MOE of 300 (due to the use of a LOAEL) is required for inhalation exposures .

#### **E. Recommendation for Aggregate Exposure (food, water and residential) Risk Assessments**

Since there are no residential uses, aggregate exposure risk assessments will be limited to food and water.

For **acute** aggregate dietary exposure risk assessment, combine the high end exposure values from food plus water.

For **chronic** aggregate dietary exposure risk assessment combine the average values from food plus water.

### **III. FQPA ASSESSMENT**

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and exposure data for ODM and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

The FQPA Safety Factor Committee has determined that the 10x FQPA safety factor is required for acute and chronic dietary exposure for oxydemeton methyl. For details, refer to the FQPA Safety Committee Report dated August 6, 1998.

**IV. ACUTE TOXICITY**

<b>Study Type</b>	<b>Animal</b>	<b>MRID No</b>	<b>Results</b>	<b>Toxicity Category</b>
81-1: Acute Oral	Rat	40779801	Female: LD <sub>50</sub> = 48 mg/kg	I
81-2: Acute Dermal	Rat	00143350	Female: LD <sub>50</sub> = 112 mg/kg	I
81-4: Primary Eye Irritation	Rabbit	00151801	Slightly irritating	III
81-5: Primary Dermal Irritation	Rabbit	00151801	Non-irritating	IV
81-6: Dermal Sensitization	Guinea Pig	40779802	Not a skin sensitizer (Beuhler)	N/A

## V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints and margins of exposure for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE <sup>a</sup>
Acute Dietary	LOAEL=2.5	Decreased Plasma, RBC and brain ChE activity in males	Acute Neurotoxicity in the rat	NA
	UF=300	Acute RfD = 0.008 mg/kg/day		
Chronic Dietary (Non-cancer)	NOAEL=0.0125	Erythrocyte and brain ChE activity	Chronic-Dog	NA
	UF=100	Chronic RfD = 0.000125 mg/kg/day		
Carcinogenicity (Dietary)	Classified as a “Not Likely” human carcinogen.			
Dermal Absorption	Calculated to be 50.4% for males and 51.8% for females			
Short-Term (Dermal)	Dermal NOAEL=5.0	Decreases in RBC and brain ChE activity	7-Day Dermal Toxicity-Rat	100
Intermediate-Term (Dermal)	Dermal NOAEL=0.3	Decreased brain ChE activity	14-Day Dermal Toxicity -Rat	100
Inhalation (any time period)	Inhalation LOAEL = 0.098 mg/L	Clinical signs (tremors)	Acute Inhalation - Rat	300 <sup>b</sup>

a = MOEs are of occupational exposure only; no residential uses at this time.

b = MOE 300 required due to use of a LOAEL.